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OCCUPATIONAL ALLERGIC CONTACT DERMATITIS AND ASTHMA DUE TO A SINGLE LOW MOLECULAR WEIGHT AGENT

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Running head: contact dermatitis and asthma from chemicals

Case study

Two tables, one figure

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Introduction

Contact dermatitis allergens are low molecular weight chemicals that are not immunogenic by themselves because they need to bind to epidermal proteins in order to act as immunogens¹. The agents that cause occupational asthma (OA) are categorised as high molecular weight (HMW) and low molecular weight (LMW) agents according to whether their molecular weight is above or below 1 kD². Sensitisation to environmental allergens, which are HMW glycoproteins of either animal or vegetable origin, is established by the positivity of specific cutaneous tests or the presence of specific IgE in the serum³. This IgE-mediated allergy has also been identified for some LMW agents responsible for OA, such as anhydric acids⁴, reactive dyes^{5, 6}, platinum salts^{7, 8}, and other metals^{9, 10, 11}.

Metals have been reported to cause both allergic contact dermatitis (ACD) and OA in the same factory^{12, 13, 14}. However, the relationship between the pathophysiological mechanisms of these two manifestations from a single causative agent is not well-known. To our knowledge, except for metals, few cases of ACD associated with OA from LMW agents have been reported in previous studies^{15, 16, 17}. The estimation of the occurrence of ACD associated with OA from a single LMW agent is needed to assess whether the pathophysiological mechanisms of these two symptoms are linked with each other or not. In this study, we first estimated the occurrence of ACD associated with OA from a single LMW agent in workers with contact dermatitis (CD). Then we reported cases we found in order to identify high-risk occupations to contribute to prevention of new case appearances.

Methods

Population

The study population consisted of all new cases of CD diagnosed at the Occupational Health Medical Consultation from January to December, 2005. The Occupational Health Medical Consultation provides consultations in the Department of Dermatology of a public referral

hospital which is located in the centre of Marseilles. To be eligible for the study, patients had to be workers of at least 16 years of age at the time of diagnosis. An eligible 234 subjects were asked about skin and respiratory symptoms. When these symptoms recurred during work exposure and improved during rest-days, they were considered as work-related CD, which was diagnosed according to the criteria of the American Contact Dermatitis Society¹⁸. OA was diagnosed if the criteria proposed by the American College of Chest Physicians were met¹⁹. Our protocol was approved by the Commission Nationale de l'Informatique et des Libertés (n° 748653).

Skin-prick tests and patch tests

Ten patients, found with both work-related CD and respiratory symptoms, underwent skin-prick tests and patch tests. Skin-prick tests included common environmental allergens and were considered positive if the mean wheal diameter was 3 mm or greater. Atopy was diagnosed on the presence of at least one positive skin prick test. The patch test procedure included the European standard series and, depended on the clinical examination and oriented anamnesis, supplementary allergen panels and specific patch testing. The patch tests were applied and analyzed according to standard protocols: allergens were applied in Finn chambers, reinforced with adhesive tape, evaluated at 48 and 72 hours, and scored according to the International Contact Dermatitis Research Group guidelines²⁰. Diagnosis of ACD was based on the coherence with patch testing, localization of the eruption and history of exposure to an occupational agent. Two irritant contact dermatitis and 9 ACD cases were observed. Among them, three patients with both ACD and expiratory troubles caused by a single causative agent were found. Two were caused by 2-hydroxyethylmethacrylate (HEMA) (subject N°.1, N°.2), and one by bisphenol A diglycidylether (DGEBA) (subject N°.3).

Blood sampling, lung function and provocation tests

Blood was sampled for total IgE measurement from the 3 subjects presenting ACD and expiratory troubles caused by a single substance. Lung function and provocation tests were

carried out on 2 of them. Baseline lung function comprised measurement of one-second forced expiratory volume (FEV₁), and forced vital capacity (FVC) with a dry seal spirometer according to the recommendations of the European Respiratory Society²¹. Bronchial hyperresponsiveness was assessed by inhalation of methacholine chloride. A 20% fall in FEV₁ compared to the baseline value was defined as bronchial hyperresponsiveness, and the provocative dose (mg/ml) of methacholine chloride causing a 20% reduction in FEV₁ was measured. To confirm the cause of the OA, specific inhalation challenge (SIC) tests were carried out for subjects N°.1 and 3 according to existing recommendations²². Subject N°.2 didn't want to undergo respiratory investigations. The SIC test was considered positive if there was a fall of over 15% in FEV₁ within one hour from the challenge (immediate reaction) or a fall of over 20% later (late reaction) compared to the values before the challenge and to the concurrent values of the placebo test.

Case reports

Details of age, gender, personal and medical data, and occupational exposure of the 3 subjects with both ACD and expiratory troubles caused by a single causative agent are given in Table 1. Results of total IgE and methacholine challenge are in Table 1. Results of patch-tests are indicated in Table 2.

Subject N°.1

A 44-year-old non-smoking female beautician had been working in a hairdressing salon for 20 years. She had intolerance to pieces of costumes jewellery, and developed urticaria when using make-up pencils. Her daughter had asthma. We investigated her fifteen months after she developed finger dermatitis and expiratory symptoms, (Table 1). The symptoms were work-related and improved during weekends and holidays. The patient associated the cutaneous and respiratory symptoms with the introduction of a nail prosthesis method using new solvents and resins. Her job required that she wore false nails for promotional purposes. The dermatitis

did not improve with natural rubber latex gloves. When we saw her, we observed a fissured purulent pulpitis on all her fingers. We did not hear any asthmatic rales from her lungs.

Patch testing revealed that the patient had a patch reaction to HEMA in the methacrylate series (Table 2). Due to the severity of her CD, she could not continue her work, so Peak Expiratory Flow (PEF) monitoring could not be carried out. A SIC to HEMA without hardener was performed. She developed an early asthmatic reaction (20 % drop in FEV₁) 60 min after challenge with dysphonia (Fig 1). A placebo test performed with lactose was negative. These results lead to the diagnosis of ACD and OA induced by HEMA.

Subject N°.2

A 22-year-old beautician came to the consultation with cutaneous and respiratory complaints that had started 4 months after she began her activity of nail prosthesis. She had had asthmatic bronchitis and seasonal spring rhinitis in her childhood, and her mother was asthmatic. However, there was a clear association with her occupational activities, since her symptoms decreased during weekends and cleared completely on holiday. She worked during the days before our clinical examination which revealed sneezing, wheezing and dermatitis localized on the hands, forearms, low neckline, and thighs. She attributed the troubles to activated ultraviolet gel and to acrylic liquid used daily. A patch test with methacrylate series was negative. Positive patch tests (Table 2) were obtained from activated ultraviolet gel and from acrylic liquid. According to material safety data sheets obtained from the manufacturer, the products contained HEMA. The patient did not wish to undergo further respiratory investigations because she decided to change occupation before these tests could be done. When the patient changed job, all her symptoms and signs resolved. The diagnosis of ACD from HEMA was established. Thus, the association between work related wheezing and workplace exposure to agents known to cause asthma defends the diagnosis of OA, even if it could not be proven.

Subject N°.3

A 39-year-old epoxy resin applicator had skin lesions on his hands, forearms, and legs, which had been progressively worsening for 3 months. The products he used at work contained DGEBA. The first lesions appeared one month after he began this job. They improved after 15 days of rest but relapsed soon after his return to work. About 2 or 3 weeks after the skin lesions appeared, he had nocturnal bouts of respiratory difficulties, which occurred during working periods. He had no personal nor familial atopic disease (Table 1). Patch testing (Table 2) showed allergic reactions to DGEBA in the standard series, from professional epoxy resins and from hardeners, based on DGEBA products. After the patient spread DGEBA he used at work on a plate continuously for 30 minutes, the specific bronchial provocation test was negative on FEV₁ but it provoked a severe coughing attack, so he refused to repeat the test on the following day. A control test using an aerosol of lactose powder did not lead to any respiratory symptom or decrease in ventilatory function. We concluded that he had ACD and probably irritant bronchial syndrome induced by epoxy resins.

Discussion

In our study, the positive patch test and SIC (particularly for subject N° 1), together with the occupational and clinical data, display concomitant ACD and OA as a result of sensitisation to acrylic and epoxy resins. Subject N°.2 was not tested through the airways with HEMA and subject N°.3 had cough but no reduction in FEV₁ following respiratory exposure to epoxy resins. For this last subject, the cough might have been of an irritant nature.

The first report of contact cutaneous hypersensitivity from methylmethacrylates was for a dental surgeon in 1948²³. Later, it was shown that respiratory hypersensitivity could also be induced by cyanoacrylates, methacrylates and methyl methacrylates^{24, 25}. In Belgium, in 1981, Kennes et al. reported the first case of OA in a factory worker who was constantly exposed to Plexiglas dusts composed of methyl polymethacrylate²⁶. In 1990, six cases of occupational asthma in cosmetologists working with artificial fingernails prompted the Colorado

Department of Health to request evaluation and control of nail salon technician's exposure to methacrylates from the National Institute for Occupational Safety and Health. Control of exposures during the application of artificial fingernails showed an elevated geometric mean ethyl methacrylate exposure value while methyl methacrylate concentrations were non-detectable on all sorbent tubes²⁷. The only observation of both ACD and OA from acrylates was reported in 2002 in Helsinki by Linström et al, and is similar to our subjects N°.1 and 2. The diagnosis of the patient, a 47-year-old female dentist, was also established by a positive patch test and SIC from HEMA, with negative prick tests from methacrylates and common environmental allergens, and a normal total serum IgE¹⁷.

Epoxy resins represent the third cause of allergic contact dermatitis, after chromates and rubber additives²⁸. More than three quarters of the epoxy resins used in industries contain the monomer DGEBA, which results from the condensation of epichlorhydrine with bisphenol A. For example, In 1959, Morris described a case of CD from epoxy resins with allergic rhinitis from inhaling epoxy resins and their amine hardeners during their processing²⁹. On the other hand, respiratory hypersensitivity induced by epoxy resins has rarely been described. In 1991, in Helsinki, Kanerva et al. published two cases of asthma to DGEBA, but did not do any work-simulated bronchial provocation test³⁰. Concerning both dermatitis and asthma from epoxy resins, only one case was reported by Kanerva et al. in 2000¹⁶, a 26-year-old concrete worker who developed contact hypersensitivity and, 5 years later, an OA from cement containing DGEBA. Prick tests with standard environmental allergens and scratch tests from DGEBA were negative, total IgE were normal. The diagnosis was confirmed by patch and SIC tests¹⁶. A cell-mediated mechanism was suggested for the dermatitis and asthma of this patient because a delayed bronchial response with a positive patch test to a LMW agent such as DGEBA was observed, and there were no suggestive signs of an IgE-mediated mechanism in this patient¹⁶. This observation seems similar to that of our subject N°.3.

In observations of ACD and OA caused by a single metal, Eslander et al.¹², and more recently, Spinelli et al.¹⁴ reported cases with allergic contact dermatitis, allergic contact urticaria, rhinitis and asthma from nickel. De Raeve et al., in 1998, reported that a subject, with allergic contact dermatitis to chromates, may develop a respiratory allergic reaction to an airborne source of this metal¹³. However, the relationship between the pathophysiological mechanisms of ACD and asthma caused by a single metal is not well-known^{12, 13, 14}.

In our 3 case reports, the observation of delayed bronchial responses with positive patch tests to LMW agents such as DGEBA or HEMA suggest that expiratory troubles could be linked to a cell-mediated mechanism¹⁶. The absence of specific IgE to acrylates, methacrylates or human conjugated acrylate-albumin in the individuals with ACD and OA³¹, the absence of positive prick tests to the same conjugated substances^{31, 32}, and the inconstant presence of specific IgE in asthma to epoxy components^{16, 17} do not suggest an IgE mechanism. Nevertheless, the absence of specific IgE or positive prick tests to a specific agent often occurs in immediate type hypersensitivity and does not indicate a mechanism of delayed type hypersensitivity.

Resin monomers might increase the oxidative stress which leads to lipid peroxidation, causing the appearance of broncho-constriction³³. In addition, a decrease of antioxidant defence may also explain why some subjects are more affected by respiratory disorders³⁴.

The results of our study show a low incidence of ACD associated with OA from LMW agents. Acrylic and epoxy resins have a highly reactive chemical configuration. It is therefore conceivable that the pathophysiological mechanisms implied in both cutaneous and respiratory intolerances are similar. Nevertheless, the rarity of reported cases of both cutaneous and respiratory suggests that variability in individual antioxidant defences may also play a role, although this theory requires further testing.

In our study, the 2 beauticians used an unventilated manicure table and the epoxy resin firm had not appropriate ventilation. Resin concentrations haven't been measured in the work place

air, but we can estimate them at high level. More preventive measures (downdraft table ventilation, good work practices and appropriate personal protect equipment) should be recommended for beauticians and epoxy resin appliers.

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Table 1. Characteristics of three subjects suffering from skin and respiratory symptoms caused by resins

		Subjects		
		1	2	3
<i>Personal</i>				
Age	44	22	39	
Gender	female	female	male	
Work	beautician	beautician	resin applier	
Smoker	no	no	no	
Atopy own/family	no/no	no/yes	no/no	
Prick positivity (standard series)	no	no	no	
Total IgE	normal	normal	normal	
Baseline spirometric measurements	normal		normal	
<i>Agent</i>				
Kind of resin used	HEMA	HEMA	DGEBA	
Time from first exposure to onset of symptoms (months)	5	4	1	
Duration of exposure before investigations (months)	15	8	3	
<i>Disease</i>				
Diagnostic (year)	ACD+OA (2005)	ACD+OA (2005)	ACD+OA (2005)	
Patch testing positivity (chemical)	Yes	Yes	Yes	
Dose of methacholine (mg/ml) causing a 20% drop in FEV ₁	0.2 mg/ml		0.4 mg/ml	
Specific bronchial provocation (max. FEV ₁ drop)	20%			

Table 2. Subject's positive patch test reaction with resins

Resin	Patch test concentration (%)	Subjects	Patch test results after 2 and 4 days
HEMA standard series	2	1	2 ⁺
Activated Ultraviolet gel *	2	2	2 ⁺
Acrylic liquid*	5	2	1 ⁺
DGEBA standard series	1	3	2 ⁺
DGEBA products*	2	3	1 ⁺

*patch test prepared by ourselves

Fig. 1. Inhalation challenge test. FEV₁ measures at defined time points from beautician (subject n°1) exposed to HEMA. After a drop of FEV₁ > 20 % of baseline, the bronchial obstruction was reversed by 200 µg of inhaled albuterol.

